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Review Article

An exploration of the natural and acquired immunological mechanisms to high-risk human papillomavirus infection and unmasking immune escape in cervical cancer: A concise synopsis

Mohammed Mohsen Mohammed[a], Zaytoon Abdulrida Ighewish Al-Khafaji[a], Nadia Mudher Al-Hilli[b]*

[a]Department of Microbiology, College of Medicine, University of Babylon, Hilla, Iraq,
[b]Department of Obstetrics and Gynecology, College of Medicine, University of Babylon, Hilla, Iraq

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Abstract

The most common STD that triggers cervical cancer is the human papillomavirus. More than 20 types of human papillomavirus (HPV) can induce uterine cervical cancer. Almost all women acquire genital HPV infection soon after their first intercourse, with most of them clearing the virus within 3 years. An immune response is necessary to clear. The first responders to HPV infection are the innate immune system elements composed of macrophages, keratinocytes, natural killer cells, and natural killer T-lymphocytic (NKT) cells. Cytotoxic T lymphocytes (CTLs) comprise the second line of defense and kill HPV16-infected cells expressing various peptides derived from their transforming early viral oncoproteins, mainly E2•E6. Even though HPV can manage to trick away our immune systems, first of all, it is important to emphasize that HPV replication does not kill the host cells. It does not replicate viral antigens or cause inflammation. The HPV16 E6 and E7 genes suppress host cell type 1 interferons (IFNs), which are detectable after infection. The patient may have immunological tolerance; hence, there are no costimulatory signals from inflammatory cytokines like IFNs during antigen recognition. Evidence shows that HlA class I generations have been inhibited by HPV16 E5, which could protect this tumor cell from CTL attack. HPV16 E7 is responsible for initiating immunotolerance and increasing regulatory T cells (Treg) to repress immunological regression. Evasion from immune system protection plays a critical role in the outcome of persistent HPV infection and the development of cervical cancer. Vaccination against HPV16 and 18 during adolescence is the most effective method for preventing cervical cancer in women, considering the immunological processes involved.

Keywords: *Acquired immunity, Human papillomavirus, Immune escape, Natural immunity, Uterine cervical cancer*

Introduction

It is hypothesized that specific human papillomavirus (HPV) is accountable for 30%–50% of penile cancers, 60%–90% of vaginal cancers, 25%–30% of oropharyngeal cancers, and virtually all (99%) cervical cancers [1]. HPV is a viral infection that has been shown to cause the growth of abnormal cells in the cervix of the uterine tract, resembling condylomas and papillomas that develop in mucosal tissues or squamous epithelium of the skin [2]. A total of 180 HPV genotypes have been observed, with over 40 alpha-genus genotypes capable of infecting the mucosal or cutaneous epithelium. High-risk are the 15 HPV varieties comprising the alpha genera: HPV16, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 [3]. Incorporating the HPV genome into the host genome allows human keratinocytes (KCs) to produce HPV16 E6 and E7 proteins, which is essential for malignancy development [4]. The E6 and E7 proteins hinder the activities of Rb and p53, leading to the buildup of genetic alterations in the host genome and unrestrained cell growth. [5]. Multiple research studies have provided evidence that over 80% of women throughout their entire lifespan are contaminated with HPV, and over 50% of adolescent women, after their initial sexual encounter, are infected [6]. Approximately 90% of the infections resolve themselves naturally within 3 years,

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***Address for correspondence:** Dr. Mohammed Mohsen Mohammed, Department of Microbiology, College of Medicine, University of Babylon, Hilla, Iraq.
E-mail: med122.mohammed.muhsin@student.uobabylon.edu.iq

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whereas a mere 10% endure and 1% progress to cervical cancer. Malignant progression lasts longer because HPV is not so virulent that it can standardize cell-to-cancer cell changes that have taken place for more than 10 years. The process illustrated in Figure 1 requires persistent infection with HPV E6 and E7 proteins. Additional indicators of risk, such as having many pregnancies, cigarette usage, using contraceptive medication for an extended period, and having a weakened immune system, are believed to contribute to the persistence of HPV infection, thus promoting the carcinogenic process [7]. As stated, immune responses eliminate HPV infection in most healthy women [8]. Adaptive and innate immunities are distinct immune systems that collaborate to thwart viral infection. Adaptive immunity reacts exclusively to particular HPV proteins and consists of two arms: the type 1 helper T (Th1) cell response and the type 2 Th2 response. Th1 cells secrete interleukin-2 (IL-2) and interferon-gamma (IFN-γ) that aid in activating macrophage and cytotoxic T lymphocytes (CTLs), respectively, representing cell-mediated immunity (stimulate CTLs to eliminate virus-infected cells) [9]. Meanwhile, Th2 cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13, which help in the proliferation and differentiation of plasma cells to B cells, thus switching to diverse antibody subsets representing humoral immunity. Immune response targeting HPV16 E2 and E6 proteins is critical for eradicating HPV infection during infection [10].

HPV infection harbors several immune evasion mechanisms that may promote cancer development [11]. Remarkably, people diagnosed with high-grade cervical intraepithelial neoplasia (CIN) seldom have Th1 immune responses, and these immune responses are impaired among individuals with cervical cancer [12]. Inducing Th1 immune responses against HPV antigens is essential for avoiding the emergence of neoplasia. The recruitment of the defense system against HPV infection and the mechanisms by which HPV evades this system are the subjects of this review. This investigation aims to develop innovative immunotherapeutic interventions for cervical cancer by exploring immune evasion strategies.

Interactions between the human papillomavirus and the innate immune system

HPV could penetrate the skin via layers that have been weakened or damaged [13]. The epidermis, the outermost layer of the skin, is the first barrier to protect people from viral infections. It consists of basal germinal, granular, and keratinized layers [14]. KCs function as nonprofessional antigen-presenting cells (APCs) and play a role in the innate immune system by presenting antigens and producing Th1 and Th2 cells through CD4+ and CD8+, respectively [15]. Moreover, KCs and other nonprofessional innate immune cells have the ability to produce several pattern recognition receptors (PRRs) that have the potential to recognize, identify, and react to different viruses referred to as pathogen-associated molecular patterns along with recognize danger signals called damage-associated molecular patterns [16]. The Toll-like receptor (TLR) family may be found on the surface of the cell or inside endosomes, as indicated by their expression [17].

The TLR9 receptor is an immune receptor located in endosomes; it recognizes explicitly unmethylated CpG double-stranded DNA viruses, such as HPV [18]. TLR9 receptors have the potential to trigger cellular signaling pathways, which in turn may result in the production of cytokines and type I IFN (IFN-I). It has been shown that activation of TLR9 in KCs results in the production of many cytokines, including tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), cytokines CCL2, CCL20, and CXCL9, as well as IFN-I [19]. TLR9 is a type 1 transmembrane protein. Structurally, TLR9 has an N-terminal domain consisting of repeated LRRs (leucine-rich repeats), followed by a domain

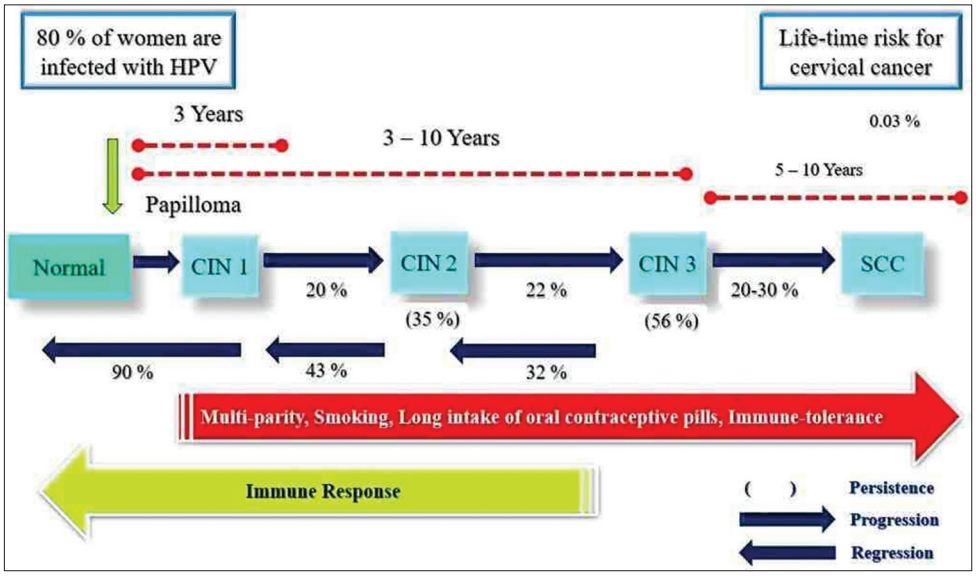

Figure 1: The progression of human papillomavirus infection to the development of cervical cancer. Cervical intraepithelial neoplasia refers to abnormal changes in the cells of the cervix. SCC is an abbreviation for squamous cell carcinoma, a cancer that develops in the squamous cells of the cervix. HPV: Human papillomavirus, CIN: Cervical intraepithelial neoplasia

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including transmembrane regions and cytoplasmic TOLL/TIR domains [20]. The expression of the TLR9 receptor is limited exclusively to plasmacytoid dendritic cells (pDCs) and B lymphocytes [21]. Upon binding to its ligand, TLR9 initiates the activation of MyD88, forming a complex with the IRAK family protein; this complex then causes a signaling cascade that ultimately activates nuclear factor-κB (NF-κB) and AP-1 transcription factors [22]. These factors are responsible for inducing immune responses to invading pathogens, as shown in Figure 2.

Furthermore, TLR9 expression is suppressed by the HPV16 E7 oncogene through the NF-κB canonical pathway. The oncoprotein involves an inhibitory complex NF-κB p50–p65 anchored to a new cis-element in the TLR9 promote. Concurrently, when HPV16 E7 is present, ERα (estrogen α) binds to an adjacent cis-element in the same estrogen-responsive element (ERE) promoter. Transcription is strongly inhibited by the ERα binding to the p65 subunit in the peri- or intranuclear region. Moreover, a chromatin-repressive complex, including HDAC1 deacetylase and JARID1B demethylase, was found. The catalytic components engage with ERα, resulting in the downregulation of TLR9 expression [23]. TLR9 expression is reduced, leading to an immunosuppressive state that hampers interferon generation and hinders immune surveillance via cytokine responses, as illustrated in Figure 3.

Deciphering the keratinocytes modulation in the initial phases of human papillomavirus pathogenesis

The basal layers of uterine cervical epithelium are the ultimate target and milieu for certain HPVs, where it infects KCs and possibly stem cells. Since KC is the main target of HPV, its role in the initial phase of HPV infection has been emphasized [24]. KCs are immune sentinels of the innate immune system. KCs expressing many TLRs, such as TLR-1, -2, -4, -5, and -6, were found at the cell surface in female genital tracts or inside endosomes (TLR-3 and 9) [25] visualized in Figure 2. Specifically, TLR-3, TLR-7, TLR-8, and TLR-9 detect double-stranded RNA (dsRNA), detect single-stranded RNA (ssRNA), and detect double-stranded DNA in sequences rich with CpG. Endosomal TLRs fight viral infections and identify viral genetic material; stimulating these receptors increases cytokine production, creating a highly proinflammatory environment [26]. HPV can alter the amounts of cytokines to evade the immune system. This technique primarily aims to suppress the proinflammatory response in cervical KCs [27]. Cytokines that have been either increased (upregulated) or decreased (downregulated) in the microenvironment of a tissue infected with HPV [28], as shown in Figure 4.

IFNs play a crucial role in the innate immune system, aiding in the protection against viruses through various

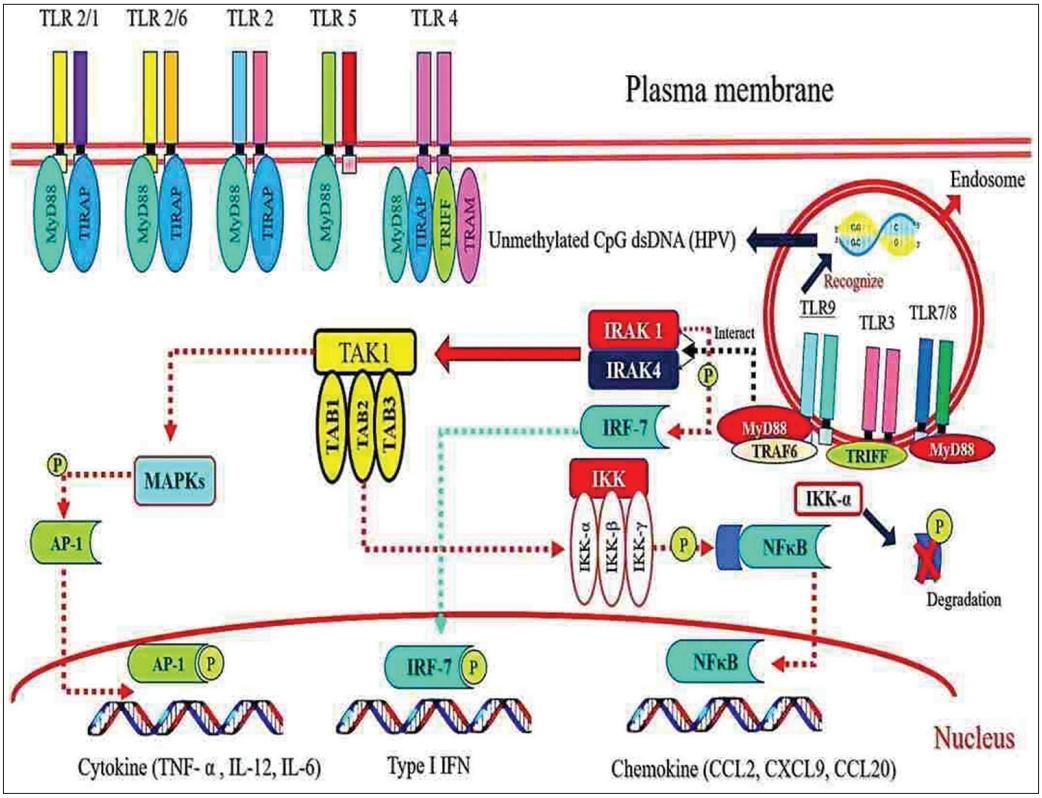

Figure 2: A comprehensive examination of the Toll-like receptor 9 (TLR9)-mediated signaling pathway. TLR9 binds to its ligands inside endosomal compartments, such as CpG-oligodeoxynucleotide (ODN) viral dsDNA (human papillomavirus). The TIR domain of TLR9, located in the cytosol, attracts the adaptor protein MyD88 and other signaling molecules, including IRAK-4 and TRAF6, which are necessary to form the signaling complex. Transcription factors such as interferon regulatory factor-1 (IRF-1), IRF-5 (not seen in this diagram), and IRF-7 are further brought into the complex and stimulated, as the text explains. The intricate structure then triggers additional signaling pathways that result in the activation of nuclear factor-κB and AP-1. These activated transcription factors stimulate a variety of genes associated with immunity. NF-κB: Nuclear factor-κB, TLR9: Toll-like receptor 9, TNF: Tumor necrosis factor, IL: Interleukin, IFN: Interferon, IRF: Interferon regulatory factor

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pathways that involve antiviral, antiproliferative, and immunostimulatory mechanisms. There may be a connection between the regression of HPV lesions and an interferon response. Nevertheless, the presence of HPV oncoproteins diminishes the KC's release of IFN and MCP1 [29].

HPV16-positive individuals with premalignant lesions have a higher response rate to IFN-α therapy, especially when E7 gene transcripts are at a low level [30]. KCs harboring episomal copies of HR-HPV exhibit several dysregulated genes associated with chemotaxis and proinflammatory processes [31]. Conversely, the genes that are downregulated are implicated in natural and acquired immunological responses and KC differentiation. These findings highlight the significance of the KC in triggering the immunological responses against HPV and its role in connecting to the adaptive immune response [32].

Strategies by which keratinocytes avoid immune system attacks

Most patients spontaneously resolve HPV-associated lesions within 1 to 2 years, as shown in Figure 1, emphasizing that the immune system of that host controls HPV infection. However, even with the activation of the immune system, HPV-related lesions may last for an extended period, ranging from months to perhaps years, before showing signs of regression [33].

In addition, there is a 6- to 12-month latency period before anti-HV antibodies can be detected in the persons under infection; this indicates that HPVs have their ways of influencing and de-activating host immune response to disease and could become more serious when they combine with other risk factors. Weakened immune status (e.g., renal transplant or HIV) is a risk factor for chronic HPV infection, affecting 4%–28% of individuals with long-lasting high-risk oral cytological abnormalities [34]. Human studies have given some positive feedback on specific major histocompatibility complex (MHC) alleles, such as HLA-DQB1 ∗ 0602 and HLA-DRB1 ∗ 1501, that increase susceptibility to persistent HPV infection, which progress in most cases toward cervical cancer [35]. Little is known about the unique biology of HLA alleles functioning to modulate HPV antigen-catalyzed cervical cancer. Here, one should remember different affinities of HPV antigens for MHC, and this variation may or may not effectively activate the immune cells specific to HPV in individuals who are protected or at risk [36].

Moreover, other deleterious events, including stochastic errors of DNA replication contingent upon sustained HPV infection, are likely to be necessary for the progression from chronic inflammation to carcinogenesis [37]. HPV probably abrogates its immunogenicity by decreasing the synthesis of antigens during the transient active viral life cycle. HPVs infect in a multi-step process, entering hosts with limited proteins that can be rapidly shuttled to the nucleus [38], hence decreasing their exposure to host immune pressure. During late-stage infection, HPVs facilitate the production of extremely antigenic capsid proteins. Most, however, the proteins are rapidly exhausted from the outer layer of the epithelium, which has a restricted quantity of antigen-presenting cells (APCs). The term used to describe these procedures is passive immune evasion tactics [39].

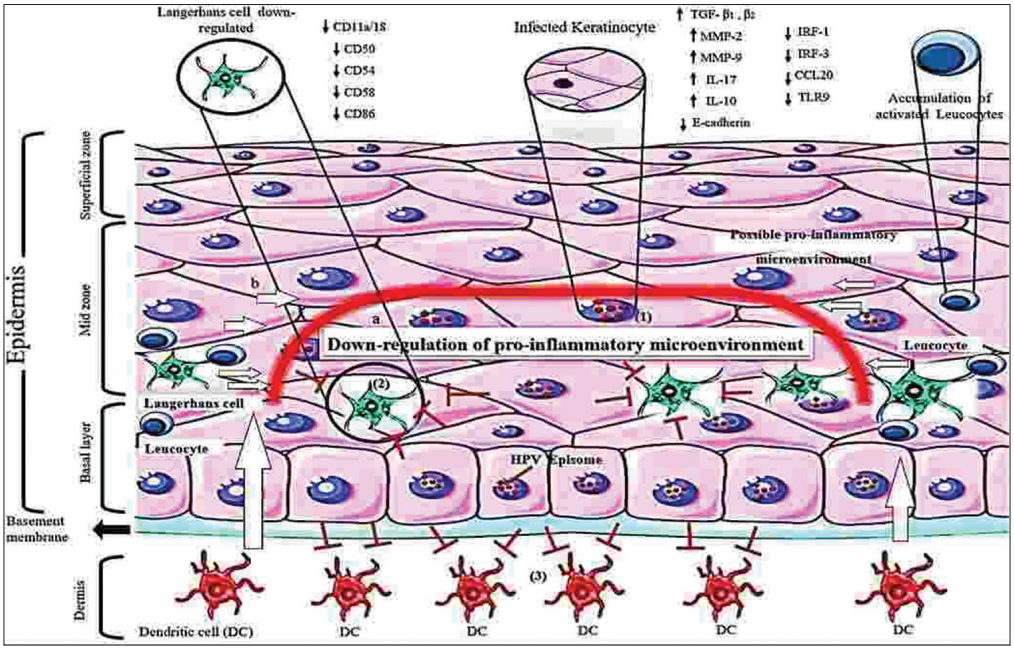

Figure 3: The human papillomavirus16 E7 oncogene suppresses the expression of TLR9 via the NF-κB canonical pathway. The NF-κB p50 and p65 components are indicated with blue (p50) or purple circles, respectively. Straight red arrows represent activation or progression to the next stage. On the other hand, the bent arrows are indicative of movement and the progressive arrow is illustrated in regard to molecules as they act with a target. IKK stands for inhibitor of kappa B kinase. P is used to indicate a phosphate group, M is used to indicate a methyl group, and A is used to represent an adenyl group. JARID1B is the name given to a protein called lysine-specific demethylase 5B. HDAC1 is the name of a protein called histone deacetylase 1. Site B refers to specific locations on a DNA molecule that are 9-10 base pairs long, where the p50 and p65 subunits interact. TLR9: Toll-like receptor 9, TNF: Tumor necrosis factor, IL: Interleukin, IFN: Interferon, IRF: Interferon regulatory factor

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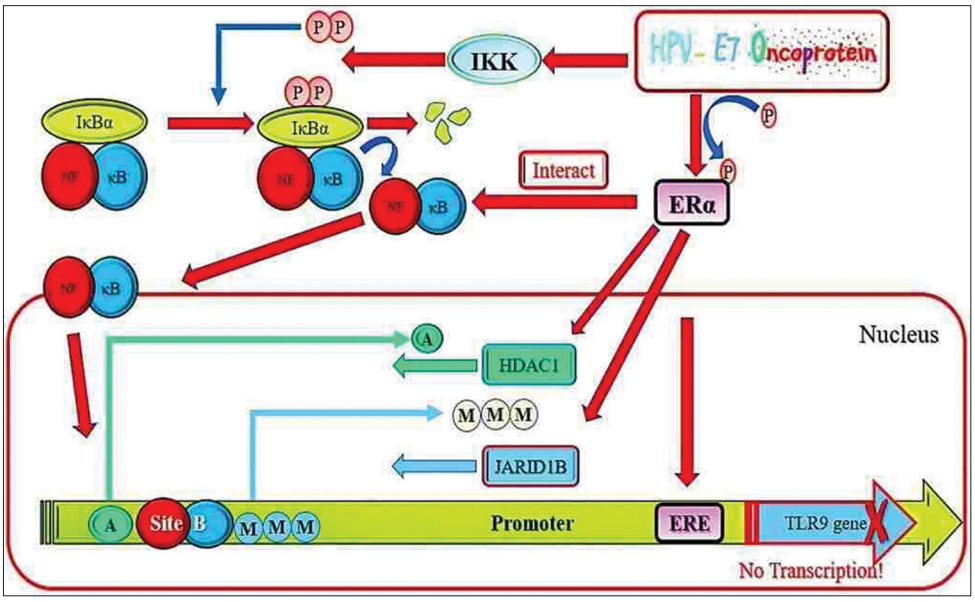

Figure 4: An illustrative characterization of the immune milieu immediately following Human papillomavirus (HPV) infection (a) The HPV is triggered in the central milieu and creates a reduction in antigen presentation, leading to the subsequent consequences: (1) Modification of the cytokine-induced inflammation reaction of keratinocytes, which serve as the first barrier toward infections; (2) impeding the stimulation and migration of Langerhans cells (LCs); and (3) Impeding the infiltration of dendritic cells (DCs) into the adjacent tissue. (b) An inflamed milieu is present in the keratinocytes surrounding the lesion. The anti-inflammatory protein inhibition (interleukin-10) and the existence of stimulated T lymphocytes distinguish this environment. TLR9: Toll-like receptor 9, ERE: Estrogen-responsive element, JARID1B: Jumonji AT-rich interactive domain 1B, HDAC1: Histone deacetylase 1, IKK beta (or IKKβ): IκB kinase beta

Moreover, HPVs can facilitate the production of HPV oncoproteins E6 and E7 effectively, thus avoiding the immune system. Furthermore, as illustrated above, it sequesters cellular immune regulator proteins so that they can act on the protein themselves, which ultimately downregulates the expression of immune-related genes and signaling pathways in HPV-infected KCs [40] [Figure 5]. This immune suppression soulmates with the consequences of oncogenic genes impairing infected cells' ability to communicate effectively with surrounding immunological cells, thereby creating an overall environment geared toward encouraging cancer.

The relevance of interferon in fighting human papillomavirus

IFN-family cytokines are essential to immunity. Epithelial cells produce type I IFNs, including IFN-alpha and beta (IFN-α and β), the first antiviral defense. They inhibit virus-infected cell growth and increase their death in infected and adjacent cells [41]. T and NK cells stimulated by cytokines produce IFN-γ, which controls immunity. IFN has several antiviral components. Double-stranded RNA-dependent protein kinase PKR suppresses protein synthesis when activated by IFNs; through 2-5 oligoadenylate synthetase, IFN causes RNase L and viral RNA degradation [42]. In HPV-immortalized cells, type I and II IFNs reduce E6 and E7 RNA [43]. IFN-α inhibits HPV-16 KC immortalization. IFNs decrease HPV gene expression, whereas IFN-γ is the most efficient [44].

IFNs treat HPV-related skin, oral, and anogenital diseases; therapy efficacy varies. Not all patients react effectively. IFN-γ outperforms α and β [45]. Patients with low HPV E7 protein respond better to IFN [46].

Figure 6 depicts HPV's effects on the IFN-α and beta signaling pathways. IFNs initiate JAK-STAT signaling via cell surface receptors; during activation, JAK1 and tyrosine kinase 2 (TYK2) phosphorylate cytoplasmic IFN receptor tyrosines; this allows SH2 domain-bound STAT1 and STAT2. In the presence of interferon-stimulated gene factor-3 (ISGF3-gamma), phosphorylated, dimerized STATs attach to the nucleus ISRE. This complex binds ISRE to induce IFN-responsive gene transcription [47]. There are two ways high-risk HPV E6 oncoproteins block IFN signalling: HPV18 E6 protein physically interacts with TYK2 in the TYK2-IFN receptor. E6 prevents TYK2 from interacting with the receptor and phosphorylating JAK and STAT. HPV-16 and 18, E6 disrupt IFN signalling more than low-risk HPV-11 E6. HPV-16 E6 protein binds and inhibits IRF-3 [48].

Figure 4 shows HPV-16 E7 binding ISGF3 transcription complex p48. The interaction involves E7's pRB-binding region. The function of E7 is to prevent ISGF3 and IFN activation. A study conducted by Rho *et al*. [49] observed that HPV-16 E7 inactivates IRF-1. IRF-1, a key IFN signaling intermediate, may inhibit IFN proliferation. Papillomas resistant to IFN and CINs may have elevated levels of the E6 and E7 proteins. HPV-16 E6 and E7 levels rise in CIN, leading to resistance to IFN [50]. The levels of IFN-β and γ were lower in CIN and cancer compared to the cervical epithelium.

The task of professional antigen-presenting cells

LCs are specially designed APCs that are found in the epidermis. They have a vital function as immunological

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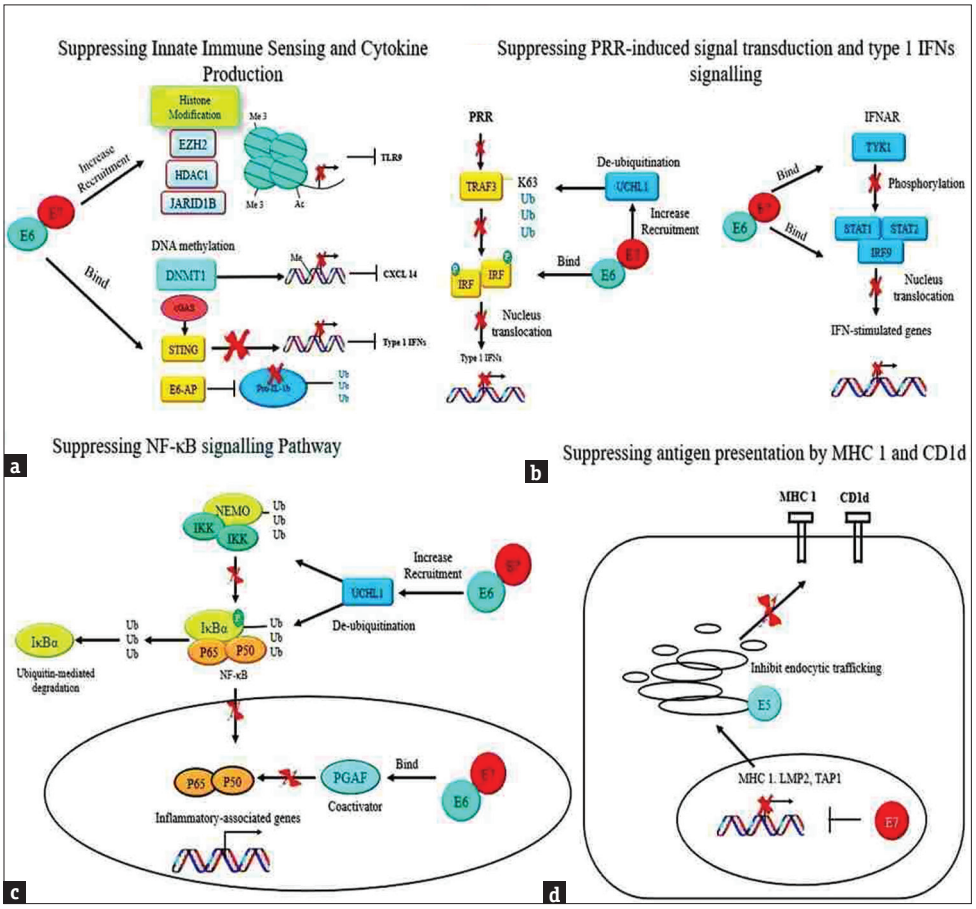

Figure 5: Complex immune evasion stratagems in keratinocytes employed by human papillomavirus (HPV) oncoproteins. (a) Inhibition of TLR9 and CXCL14 promoter activity using histone-modifying enzymes (EZH2, HDAC1, and JARID1B), as well as a DNA methyltransferase enzyme (DNMT1) is caused by high-risk (HR) HPV E6 and E7 oncoproteins. Interestingly, E6 and E7 proteins also interact with an adaptor protein STING for a likely role in host antioxidant defense response. This interaction results in the inhibition of the cGAS-STING cytosolic DNA sensing axis and cleavage pro-IL-1β. (b) High-risk HPV E6 and E7 suppress the signaling of pathogen recognition receptors (PRR). This effect results from the inhibition of Ubiquitin C-Terminal Hydrolase L1 (UCHL1) and consequent TRAF3 activation. Furthermore, E6 and E7 bind to the Nucleus interferon regulatory transcription factor (interferon regulatory factor [IRF]), compromising its capacity for transcribing. E6 and E7 attach to tyrosine kinase 2, which blocks the phosphorylation of STAT1 and STAT2 that forms an interferon signaling complex in interferon (IFN-α/β) receptor-dependent signal transduction. They also interact with IRF9, thus impeding the association to phosphorylated STAT1 and STAT2. It is important for the activation of IFN-stimulated genes. (c) The movement of NF-κB in the nucleus is almost completely prevented both by High-risk HPV E6 and subsequently, to a lesser extent, by HPV52E7, which increases UCHL1 expression. In the Nucleus, E6 and E7 interact with P300/CBP-associated factor (PCAF), which may be an NF-κB coactivator. This interaction results in the inhibition of the NF-κB signaling process. (d) Suppression of critical genes such as MHC I, LMP2, and TAP1 is due to an interaction between high-risk HPV E7 protein and the MHC I promoter. Nonetheless, E5 plays a crucial role by binding to host proteins in the endoplasmic reticulum and Golgi complex, leading to diminished production of MHC I and CD1d molecules, which ultimately prevents their transportation onto the cell surface. IFN: Interferon

sentinels [51]. Upon identification of the antigen, its transfer to secondary lymphoid organs initiates the activation of adaptive immune cells [52]. The interruption of transit of LCs to and from the epidermis assists in the immune evasion by HPV [53] [Figure 7a]. The existence of LCs inside tumours has been shown to possess a negative link with the seriousness of HPV16+ cervical and head and neck cancer lesions [54]. The downregulation of the chemokine CCL20 is the reason why LCs are not attracted to sites of inflammation. HPV16 E6 and E7 production results in the suppression of CCL20 via the inhibition of the NF-κB signalling cascade [55].

Furthermore, HPV-related tumours have decreased expression of E-cadherin in comparison to the normal epidermis. E-cadherin is a cohesive molecule that facilitates the retention of LCs in the epidermis, hence facilitating the absorption of viral antigens. Research conducted by [56] indicates that HPV16 E7 inhibits the production of E-cadherin by causing methylation of the E-cadherin promoter.

Likewise, the presence of CCR7 on moving DCs is decreased in HPV-related cancers, which decreases the ability of DCs to migrate to secondary lymphoid tissue [57]. Overall, this evidence suggests that the movement of LCs is hindered in epithelium infected with HPV. Thus, the insufficient activation of effector T cells might be partially due to a lack of antigen-presenting LCs. It is important to note that determining the trafficking of LCs will be vital in terms of evaluating whether the therapeutic intervention could potentially ameliorate defects in anti-HPV immune responses associated with HPV-driven malignancies [58]. Thus, it appears that APCs in HPV-infected epithelium tend toward an immature phenotype characterized by decreased cell surface MHC and lost costimulatory markers such as CD80

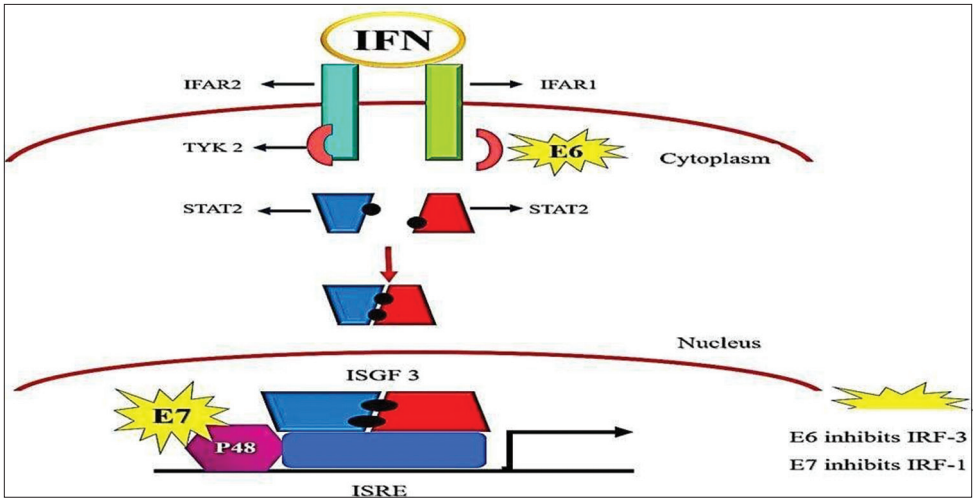

Figure 6: Type I interferons attach to their receptors, causing tyrosine kinase 2 to phosphorylate tyrosine and activate STAT1 and STAT2. These activated proteins form dimers and bind to the ISRE (interferon-stimulated response element) with p48 to activate interferon-responsive genes. Human papillomavirus E6 and E7 suppress interferon-mediated gene expression by interacting with signaling pathway components. IFN: Interferon, IRF: Interferon regulatory factor

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and CD86. Debilitation of this expression results in a lower capacity for DCs to activate an antigen-specific T-cell immune response [Figure 7a]. Tumor cells secrete immunosuppressive substances that hinder the maturation of DCs in numerous malignancies. T-lymphocytes require IL-10, transforming growth factor-β (TGF-β), IL-6 mixed with indomethacin and prostaglandin E2 (PGE2), as well as granulocyte-macrophage colony-stimulating factor; these are some of the few factors included in this procedure [59] [Figure 7c and d]. These factors are major contributors in guiding the immunosuppressive milieu, either enhanced or abrogated in HPV-related cancers. We reviewed existing studies that have already investigated the elevation of LC maturation as a treatment approach to fight infection by HPV. Two immunostimulants, polyinosinic:polycytidylic acid (Poly I:C) and the biologic IRX-2 generated from cells and based on cytokines, were able to increase the expression of MHC and costimulatory molecules on LCs that were previously exposed to HPV16. In addition, it was shown that both Poly I: C and IRX-2 may increase the migration of LCs to secondary lymphoid organs by upregulating the expression of CCR7 on LCs [60]. Due to these modifying actions, LCs regained their ability to stimulate CD8+ T cell immunological responses against HPV16-derived peptides [61]. Indoleamine 2, 3-dioxygenase 1 (IDO1) is an enzyme that suppresses the immune response against tumors [62]. However, further research is required to examine the source and purpose of these IDO1^{hi} APCs. They can successfully rival other immunogenic APC populations in activating T cells, resulting in the production of T cells that are unresponsive and regulatory (Tregs) [Figure 7a].

Natural killer and natural killer T-lymphocytic cells in immune system dynamics

These innate immune cells, known as NK cells, are adept at finding and eradicating cells infected with viruses. Many of these infected cells have a diminished ability to present MHC I molecules on their surface. Curiously, NK cells are themselves protected from death by CTL using an exciting strategy. In individuals with chronic HPV infections and cervical cancer, NK cell functionality is notably impaired, as indicated by the reduced expression of various NK-activating receptors, such as NKp30, NKp44, NKp46, and NKG2D [63]. Recent findings have shown the role of tumor-derived immune checkpoint molecules, such as IDO, in reducing NK cell function within HPV+ cervical lesions [64,65]. As previously mentioned, IDO+ DCs may be located in the skin due to the ongoing presence of HPV16 E7 expression. IDO expression in the cancer microenvironment is also known to be increased by activated macrophages, APC, and tumor cells [66]; this indicates that these cells may impede the function of NK cells in HPV-positive cervical lesions.

In addition, it has been demonstrated that the changes in IL-10 and type I IFN levels within HPV lesions have a detrimental effect on the maturation and functioning of NK cells [67]. Collectively, these data point toward the active participation of tumor-derived immunosuppressive substances in disrupting NK cell function within a growing primary allogeneic tumor [Figure 7b]. NKT cells form a distinct group of T cells that integrate aspects of T cell and NK cell functions. A well-characterized subset of these cells has a semi-invariant T- cell receptor (TCR). Detection of CD1d molecules leads to significant production of proinflammatory cytokines. These molecules have lipid antigens on APCs and cancer cells [68]. Because of these properties, NKT cells are generally associated with the innate branch of the immune system. AG presented NKT cell activity analysis in HPV-positive precancerous lesions and carcinoma of the uterine cervix. CD1d is downregulated both *in vitro* and *in vivo* by HPV16 E5 expression, which probably facilitates the immune escape of the infected cells from NKT's protective functions [69].

Furthermore, it has been shown in research involving humans with HPV+ high-grade lesions that there is an increase in the presence of NKT cells that produce IFN-γ [70]. NKT cells that generate IFN-γ may contradict the

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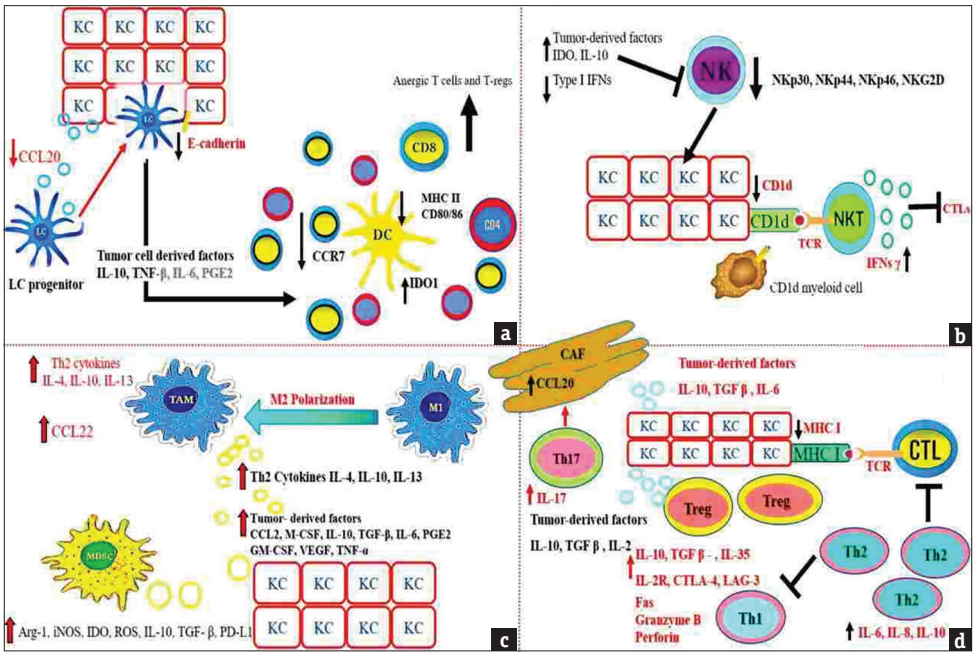

Figure 7: The association of human papillomavirus (HPV)-induced tumor microenvironment (TME) with immunosuppression is an interactional event due to the cross-talk between keratinocytes (KCs) and immune cells, which greatly facilitate these 3 processes. KCs: (a) HPV infection results in reduced expression of the chemokine CCL20 and cell adhesion molecule E-cadherin, which in turn reduces the infiltration of LCs into HPV-associated cancers. Thus, in the cancer microenvironment, both LCs and migratory DC demonstrate an immature or regulatory phenotype with a reduced potential to migrate to secondary lymphoid tissue. The reduced expression of MHC II, CD80, CD86, and CCR7 characterizes it. The other genes check what this protein performs. It also shows upregulation in IDO1. This is likely due to suppressive factors secreted by cancer cells, including interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), IL-6, and prostaglandin E2 (PGE2). (b) Inhibition of NK cell activation and tumor-killing capacity by HPV-associated tumors through enhanced production of tumor-derived factors and diminished production of type I IFNs. The stimulatory capacity of natural killer T-lymphocytic (NKT) cells is decreased, however, as the expression level of CD1d on KCs declines. A recent discovery has identified myeloid CD1d-expressing cells within the tumor microenvironment that could work as an alternate reservoir of immunosuppressive NKT cells that generate IFN-γ. (c) Tumor-derived factors, including CCL2 (upregulates Myc), M-CSF (upregulated by c_Myc) IL-10, and TGF-β from tumors upregulate the presence of tumor-associated macrophages (TAMs) in breast cancer. PGE2 favors their development into MDSCs in concert with other cytokines such as VEGFA; these suppress both innate and adaptive immunities through a number of mechanisms, including nitric oxide production to kill adjacent activated immune cells. Moreover, Th2-associated cytokines help M1 differentiate into TAMs through the phenotypic transition from type 1 to type 2. In the further development of Th2 cells, it must produce Th2 cytokines (interleukins [IL] 4/5), and TAMs will release CCL22 to attract regulatory T cells or immunosuppressor lymphocytes. MDSCs suppress effector immune response by releasing a large set of immunosuppressive molecules, including Arg-1, iNOS, IDO, reactive oxygen species, IL-10, and TGF-β in addition to PD-L1.[59] (d) Cancer-secreted elements contribute to the magnification of Tregs and the manufacture of a Th1/Th2 cell phenotype switch in the adjacent microenvironment. In addition, Cancer-Associated Fibroblasts (CAFs) recruit Th17 cells through CCL20 secretion. Collectively, these altered responses could at least partly result in impaired CTLs. HPV: Human papillomavirus, KC: Keratinocyte, IL: Interleukin, TGF: Transforming growth factor, TNF: Tumor necrosis factor, PGE: Prostaglandin E, ROS: Reactive oxygen species[59]

immunosuppressive effects and contribute to HPV-associated cancer development. Due to HPV-infected KCs' lower CD1d expression, these myeloid cells with high CD1d levels may be an alternative source of CD1d, and this activates adjacent immunosuppressive NKT cells [Figure 7b]. Furthermore, IFN-γ is known to stimulate IDO1 expression [71].

To sum up, various factors influence the effectiveness of the current Gardasil HPV vaccine. After immunization, it has been observed that the vaccine can enhance the number of NK cells and increase the expression of specific receptors such as NKG2D, NKp30, Nkp46, and ILT2 in these cells; this emphasizes other pathways. The vaccine's efficacy is enhanced by the presence of elevated levels of neutralizing antibodies [72].

Induction of cell-mediated immunity against human papillomavirus

T cells that carry the CD8 marker are designated as cytotoxic T cells. These T cells primarily use a contact-dependent strategy to destroy target cells by releasing granules such as perforin and granzyme. A study by Guo *et al*. [73] established that CD8+ lymphocytes were cervical cancer's primary immunological T cells. Similarly, another research conducted by Kadivar *et al*. [74] found that the infiltration of CD8+ lymphocytes in the epithelial layer of HPV-positive patients with normal cervical appearance is more substantial than other lymphocytes. Most cervical cancer patients' advancing phases show CD8+ reactivity to E6 as the oncoprotein, although it is not the central response to viral clearance. It has not been shown that these T cells hinder tumor development. The link between papillomavirus types and clinical cancers has highlighted immune system capabilities and their capacity to fight viral illness. Immunocompromised individuals' severe papillomavirus infection makes T-cell responses the most immune to reducing infectivity. HPV infections target epithelial cell KCs but are nonprofessional APCs; thus, noninflammatory KCs typically do not express CD80, CD8, MHC-II, or CD54 [75].

HPV infection may manifest in two distinct patterns: productive and abortive infections [76], as illustrated in Figure 8.

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It is believed that HPV infects basal cells of the squamous epithelium via minor injuries. This locoregional expression of HPV E6 and E7 proteins is confined to the basal or parabasal cell compartment, promoting epithelial proliferation [53]. Cell division makes cellular proteins responsible for replication available, and this allows HPV DNA to replicate. HPV DNA replication requires the E1 and E2 proteins, which are expressed predominantly in mitotically active cells of the mid-stratum spinosum [77]. The E4 protein is synthesized in the middle to upper layers of epithelial cells and has the ability to inhibit cell division and disrupt the keratin network within the host cell's cytoplasm [78]. The L1 and L2 proteins assemble into HPV particles that encapsulate the viral genome in capsids [79] of thermal epithelium. E4 protein may be involved in the release of HPV particles from desquamated host cells. HV genes are expressed predominantly in the outer layers of epithelial cells during productive infection, but expression of HPV ancillary proteins E6 and E7 is more common among basal cells.

During abortive infections, E6 and E7 proteins are hypothesized to be expressed most abundantly [80]. Consequently, professional APCs such as dendritic cells, macrophages, and B lymphocytes located in the dermis are unlikely to encounter HPV proteins since the infected KCs do not produce them. One hypothesis is that the microlesion caused by bacterial infection or sexual contact has triggered an encounter between APCs and HPV proteins [81]. These APCs are some of the most highly specialized cells in our immune system and can infiltrate HPV proteins into the epidermis. Notably, LCs, when exposed to HPV16 L1, become immunotolerant rather than mount an immune response [82].

APCs engulf and break down HPV proteins into peptides. After translocation of APC to lymph nodes, HPV peptides interact with MHC class 2 antigens on cell membranes [83]. It then transmits signals to naive CD4+ T lymphocytes and differentiates them as helper T lymphocytes. Thus, this mechanism enables the identification of HPV antigens and initiates adaptive immunity.

TLRs present on the cell surface recognize viral components (e.g., single-stranded DNA, virus RNA, or CpG motifs), triggering modulation of antigen processing and presentation pathways in activated DCs/macrophages. Upon activation, the immune cells release inflammatory cytokines such as IL-1, IL-6, TNF-a, and IL-12. These inflammatory signals also act as danger signals and contribute to local inflammation [84]. Figures 2 and 9 provide a schematic of an important aspect of how adaptive immune responses are started.

Naïve CD8+ T lymphocytes recognize MHC class 1-restricted antigen displayed by the same DC as MHC class 2-restricted antigen. CD8+ T cells develop into CTLs. An efficient and lasting anti-HPV immune response requires Th1-type responses (high IFN-γ and IL-2) to activate CTL and trigger effector T cells to wipe out CIN or cancer cells expressing HPV antigens Figure 9. CTLs use this sophisticated machinery to sense HPV antigens and destroy host cells that produce these virus markers. Women without CIN had more common HPV16 E6 or E7 peptide-specific CTLs when compared to women with either high-grade or low-grade lesions [85]. Indeed, women who had spontaneously cleared HPV16 or 18 demonstrated a Th1 response to the human papillomavirus type-specific E2 protein (HPV16 and 1518), as researchers revealed [86]. Another study by Clark *et al*. [87] demonstrated that CTL recognition of HPV16 E6, but not E7, was associated with clearance of HPV16.

Persistent infection in CIN leads to the development of Th2 responses, characterized by elevated levels of IL-6, IL-8, and IL-10. It has been observed that a transition from Th1 to Th2 response is linked to the advancement of lesions [88].

Regulatory T cells operate by exerting control over immune responses

Tregs are the central player in immune suppression of the tumor microenvironment. They exert their immunosuppressive effects through multiple mechanisms, prominently by secreting cytokines such as IL-10, TGF-β, and IL-35. Furthermore, Tregs can undermine immune responses through direct cellular interactions facilitated by membrane-bound TGF-β and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) [89]. In addition, they have the ability to engage in cell-membrane interactions via membrane-bound TGF-β as well as cytotoxic T lymphocyte-associated protein 4 (CTLA4), thus inhibiting the immune system [89]. Tregs are believed to originate from both natural Tregs, which are created in the thymus, and inducible Tregs, which are formed in the periphery [90]. The latter refers to the cytokines TGF-β and IL-10 made by DCs activated during priming in an environment that lowers inflammation, as shown in Figure 9 [91]. The local microenvironment is responsible for producing these cytokines derived from the host, and they contribute to the activation and proliferation of Tregs by interacting with suppressive immune subsets and cancer cells [92].

Furthermore, the stimulation plus the expansion of Tregs might be triggered by their association with M2 macrophages [93]. Patients with chronic HPV infection have a higher frequency of recruitment and activation of Tregs in their bloodstream than those who have successfully cleared the virus or have detectable E6-specific CD4+ T-cell responses [94]. Elevated Treg frequencies have been associated with poorer clinical outcomes in patients with cervical and penile cancers [95]. A significant association was discovered between a high prevalence of Tregs in cervical squamous cell carcinoma (SCC) and unfavorable outcomes [96]. Conversely, in the adenocarcinoma (AC) tumor microenvironment, a contrasting link was identified [97]. The disparity may be due to the concurrent existence of T cells with regulatory functions (Tregs) and conventional effector T cells. This condition is often uncommon in adenocarcinoma (AC) compared to SCC [98].

Humoral immune response and prophylactic human papillomavirus vaccine

Active Th2 cells, via its reservoir of cytokines, for instance, IL-4, IL-5, and IL-6, may bind to CD-40 directly or indirectly to elicit memory B cell responses to HPV antigen. HPV antibodies are generated through the transformation of B cells to plasma

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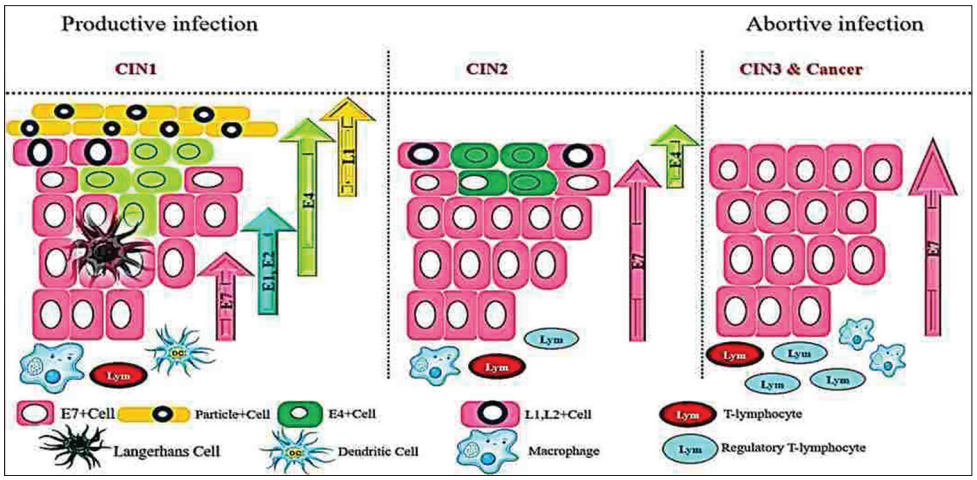

Figure 8: Human papillomavirus infection patterns and protein expression

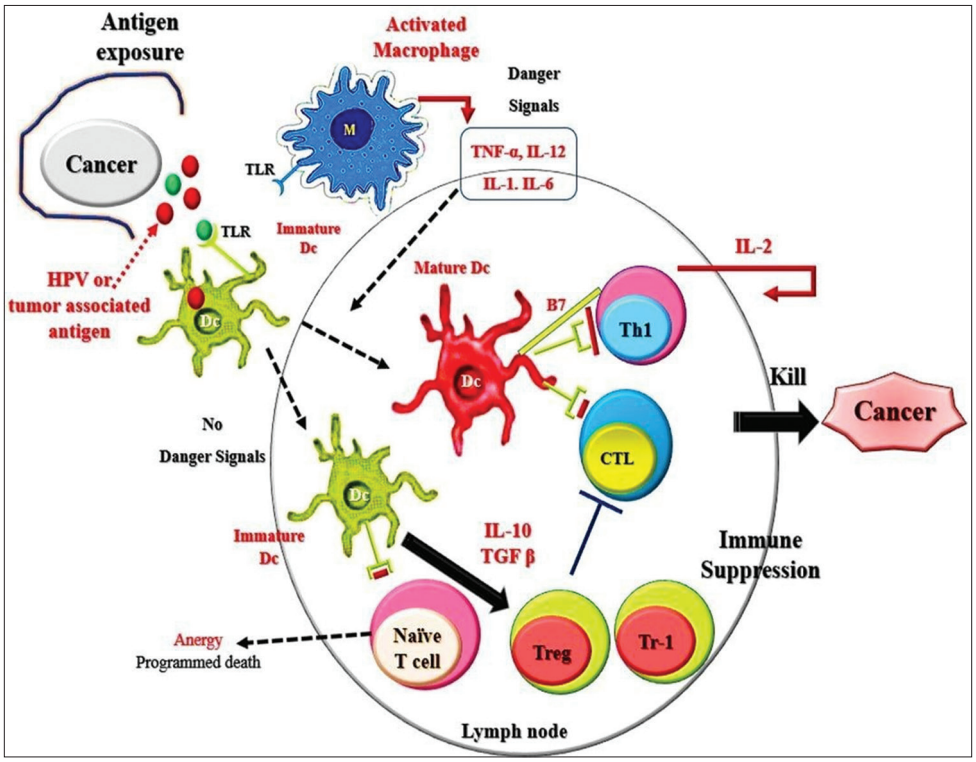

Figure 9: The initiation of cellular immune response or the development of immunological tolerance. Toll-like receptor (TLR) is an acronym for TLR, interleukin is an abbreviation for interleukin, and Transforming growth factor-β represents transforming growth factor-beta. Treg is an abbreviation for regulatory T lymphocytes, Tr-1 stands for T regulatory 1 cells, M represents macrophage, DC represents dendritic cells, Th1 denotes helper T lymphocytes of type 1, and CTL stands for cytotoxic T lymphocytes. TLR: Toll-like receptor, IL: Interleukin, TGF: Transforming growth factor

cells [98]. Specifically, antibodies that are generated against HPV16 proteins such as E4, E6, and part of L1 have been found in the blood of infected women [99]. When women have high-grade CINs or cancer, research found that they produce antibodies against HPV16 E6 and E7 [100]. Women infected with HPV16 produce HPV 16 L1 antibodies in their serum and their cervical secretions [101]. These antibodies respond to HPV16 virus-like particles (VLPs) [102]. According to a study by Stanley [103], this antibody was produced in 50%–70% of HPV16-infected women. The seroprevalence of HPV16 L1 antibodies among females aged 9–26 varied throughout four continents: North America (0% to 31%), Africa (21% to 30%), Asia/Australia (0% to 23%), Europe (0% to 33%), and Central and South America (13% to 43%) [104]. Recent research conducted in Norway found that among women aged 16–24 years, the overall incidence of HPV16 and HPV18 L1 antibodies during the 48 months was 25.0% and 13.6%, respectively, with a total of 30.4% for HPV16 and HPV18 [105]. According to these statistics, all women up to 26 years old are exposed to HPV16 or 18, approximately about one-third.

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Cervical cancer incidence and immunosuppression in HIV-positive individuals

Immunosuppression is a major factor in the evolution of cervical cancer. Cervical cancer may be a sentinel event of the progression to acquired immunodeficiency syndrome (AIDS) among HIV-positive women, as shown by some studies [106]. Data indicate that HIV-infected women who do not receive highly active antiretroviral therapy (HAART) have an increased risk of HPV infection in the cervix compared to their uninfected counterparts. In this group, sex partners of any index cases were twice as likely to be infected with HPV, four times more high-risk HPVs, and six times more multiple-type infections [107]. The correlation between the quantity of CD4+ cells and the occurrence of cervical abnormalities, as well as the intensity of HPV infection, is very significant among women who are HIV-positive but not with the levels of HIV-RNA; this suggests that the development of cancer in the cervix, which is infected with HPV, is associated with a prolonged weakening of the immune system caused by a lack of helper T cells due to HIV infection. A recent study done by Rahman *et al*. [108] discovered that HIV-positive women with abnormal cytology exhibited a greater prevalence of intermediate-risk HPV strains (HPV-53, 54, 61, and 66) and specific high-risk strains (HPV-31, 35, 45, 51, and 56), excluding HPV-16 and 18, compared to their HIV-negative counterparts, which emphasize that HPV types with lower risk levels have a more hostile attitude in an environment that weakens the immune system.

Conclusion

HPV infection may result in a range of cancer forms, and robust immune responses are essential for eliminating the virus in the majority of people. Gaining insight into the immune response to HPV is crucial for the development of preventive and therapeutic interventions for cervical cancer. KCs within the innate immune system detect and react to HPV infection via Toll-like receptors and the release of cytokines. In addition, persons who possess certain MHC alleles, such as HLA-DQB1∗0602 and HLA-DRB1∗1501, have a greater vulnerability to long-lasting HPV infections and are at an increased likelihood of getting cervical cancer. Nevertheless, HPV has the ability to elude the immune system in many ways, thereby affecting the immune system's ability to detect and respond to it. Interferons (IFNs) play a crucial role in defending against viruses. However, HPV proteins hinder the IFN signaling pathway, which leads to resistance to IFN therapy. As a result, weakened immune responses in epithelial cells infected with HPV may lead to a suppressed immunological environment in malignancies linked with HPV.

Moreover, the release of cytokines during the immune response has a substantial impact on the outcome of HPV infection. Th1 responses are connected with the regression of the virus, whereas Th2 responses are linked to the persistence of the virus. Significantly, patients with chronic HPV infection and cervical cancer have been shown to have reduced NK cell activity, which is caused by the decrease in NK-activating receptors and the increase in immune checkpoint molecules. CD8+ T cells play a crucial role in the immune response to cervical cancer, highlighting the need for a robust immune system to protect against viral infections.

Overall, Tregs have been shown in comparative cancer studies to strongly impact the immune-suppressive environment within tumors, which can affect the clinical outcomes of some types of cancers [4]. Th2 cells contribute to the activation of memory B cells for the generation of HPV antibodies as well. Nevertheless, their prevalence varies by continent. HIV-infected women not on antiretroviral treatment receiving immunosuppression may be at enhanced risk for cervical cancer progress.

Data availability statement

The datasets generated during and/or analyzed during the current study are not publicly available (because the current data have not been published yet) but are available from the corresponding author on reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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